Respondent's
Exhibit U

Thomas L.Kemper, M.D. 2/20/2008

The following report is based on my education, training and experience as a researcher and medical doctor. The opinions contained in this report are stated to a reasonable degree of medical probability.

Qualifications:

I am a Professor of **Anatomy and Neurobiology, of Pathology, and of Neurology** at Boston University School of Medicine. I received my undergraduate B.S. degree at Northwestern University in Evanston, Illinois, and my M.D. degree at the University of Illinois School of Medicine in Chicago. I have held numerous positions at various institutions in the fields of neuropathology and neurology. I have held my current position at Boston University since 1986. I have published extensively, including some of the leading texts and articles on neuropathological findings in the brains of autistic individuals. Additional information regarding my professional background is contained in my *curriculum vitae*.

Structural changes in the ASD brain:

A variety of structural changes have been reported in the brains of autistic individuals (reviewed by Bauman and Kemper, 1994, 2005; Kemper and Bauman, 1998, 2002; Palman et al., 2004; Casanova, 2007), many of which can be dated to specific times during brain development. These times extend from early embryonic stages of brain development up to adulthood. The earliest of these pathologies is a malformation in the brain stem in a unique case reported by Rodier et al. (1996). In it there was nearly complete absence of the superior olive and facial nerve nucleus, with shortening of the brain stem between facial nerve nucleus and the trapezoid body. These abnormalities could be dated to three to four week of fetal development. This timing corresponds to an increased incidence of autism following exposure to thalidomide during pregnancy (Rodier and Hyman, 1998; Miller et al. 2005). In an analysis of six brains, Bailey et al. (1998) noted additional abnormalities in the brain stem, including the configuration of the inferior olive, unusually large arcuate nuclei, and ectopic neurons on the lateral surface of the medulla. In all nine brains studied by Bauman and Kemper (2005) have shown abnormal superficial clustering of neurons in the inferior olive and in one brain there were ectopic neurons arrested in migration from the rhombic lip. All these abnormalities can be traced to neurons that are derived from a transient neuronal migratory stream derived from the rhombic lip of the fourth ventricle that is present from 8^{th} to the 20^{th} week of gestation (Sidman and Rakic, 1982).

In studies of the cerebral cortex of autistic individuals, Casanova et al. (2002, 2006) and Casanova (2007) have provided evidence in multiple cortical areas for increase number of unusually small neuronal minicolumns. These minicolumns are a fundamental building block of the cerebral cortex with their origins dating to a time from before the onset of migration of neurons to the cerebral cortex from the germinal ventricular zone

(Rakic (1995). The latter commences at about 7 weeks of gestation (Sidman and Rakic, 1982).

Malformations of the cerebral cortex have been frequently noted (reviewed by Palman et al., 2004) and can be dated to a later developmental period. In one of the brains reported by Kemper and Bauman (1998) there was a major cortical malformation called polymicrogyria that was located in the orbitofrontal region. This malformation has been shown in experimental animals to be the result of a superficial cortical lesion at a late stage of neuronal migration to the cerebral cortex (Dvorak and Feit, 1977; Dvorak, Feit and Jurankova, 1978). In the human brain this corresponds to approximately 16 to 20 weeks of gestation (Sidman and Rakic, 1982; Rakic, 1988). More subtle changes have been frequently reported. Bauman and Kemper (2005) reported indistinct cortical lamination in the anterior cingulate cortex. In other cortical areas, Bailey et al. (1998) found an increased density of subcortical neurons in four of six brains, in one an increased number of neurons in layer I, and in three disordered cerebral cortical laminar architecture. Hustler et al. (2006), in eight cases of ASD found in the cerebral cortex of three brains supernumerary neurons in layer I, six with neuronal clumping and dysplasia, three with disturbed lamination, three with increase number of subcortical neurons, and three with indistinct cortical boundary.

The focal malformations within the cerebral cortex with disordered lamination and abnormal distribution of neurons and those with an increased number of neurons in layer I and in the subcortical white matter appear to be due to two different pathological processes. The disordered lamination and abnormal distribution of neurons indicates aberrant migration of neurons within the cortical plate. In normal development, these migratory neurons first appear in the cortical plate at about seven weeks of gestation with the migration continuing until about 16 weeks of gestation (Sidman and Rakic, 1982; Rakic, 1988). The increased number of neurons in layer I and in the subcortical white matter is consistent with the persistence of a normally transient fetal and neonatal neuronal population. In the earliest stages of cerebral cortical development, there is a transient zone called the primitive plexiform layer into which the definitive neurons of the cerebral cortex migrate, separating it into the future layer I and scattered neurons in a transient subplate zone deep to the definitive cerebral cortex (Marin-Padilla, 1988). The subplate zone is unusually prominent in the human brain, where it reaches its peak development in the 24^{th} week of gestation and it is largely gone by the 6^{th} postnatal week (Kostovic and Rakic, 1990). It appears to play an essential role in the development of cerebral cortical circuits **(**Okhotin and Kalinichenko, 2003**)**. The presence of excess numbers of neurons in layer I and in the subcortical white matter in the autistic brain suggests a lack of proper resolution of this transient zone in the autistic brain, with the implication that the attendant cortical circuits may be compromised. A similar increased number of subcortical neurons have also been noted in the brains of schizophrenic patients (Akbarian et al., 1996; Eastwood and Harrison, 2003; 2005). An arrest of neurons during their migration to the cerebral cortex through the prospective subcortical white matter could conceivably also account for the ectopic neurons in this location, but not the increased number of neurons in layer I. Further, subcortical neurons associated with an arrest in migration generally occurs as cluster of cells rather than scattered individual neurons (Harding and Copp, 1997).

Another pathology that can be dated to the late prenatal period is the decrease in number of Purkinje cells in the cerebellum, the most frequently noted cellular pathology in the autistic brain (Kemper and Bauman, 1998; Palman et al., 2004; Bauman and Kemper, 2005). In those brains with a marked decrease in the number of Purkinje, there is a pallor of granule cells staining that occurs in areas with a decrease in the number of Purkinje cells (Bauman and Kemper, 2005). This pathology in the cerebellar cortex is most marked and posterior lateral part of the cerebellar hemispheres and occurs without evidence of loss of neurons in the inferior olive in the brain stem (Kemper and Bauman, 1998; Bauman and Kemper, 2005). The Purkinje cells have an intimate relationship with the axons of the inferior olivary neurons in the brain stem, such that loss of Purkinje cells at any time after birth leads to loss of neurons in the inferior olive (Holmes and Stewart 1908; Norman, 1940). Since this intimate relationship between the Purkinje cell and the inferior olive is established in the human brain at about 29-30 weeks of gestation (Rakic and Sidman, 1970), it is likely that the decrease in number of Purkinje cells occurred before this time.

In the limbic system Bauman and Kemper (1994; 2005) and Kemper and Bauman (1998) have reported that the neurons appear unusually small and more tightly packed than in age and sex matched controls. This was noted in the hippocampal fields CA1-4, subiculum, entorhinal cortex, mammillary body, amygdala, and medial septal nucleus. This pattern of change is reminiscent of an early stage of development and suggested a curtailment of maturation. Analysis of the dendritic tree with the Golgi method for staining individual neurons has also shown evidence of this curtailment in hippocampal fields CA1 and CA4 (Raymond et al., 1996). The time of origin of these changes in the limbic system has not been determined. Bauman and Kemper (1994) have speculated that the abnormalities in the hippocampus and amygdala could be fetal pattern of cell distribution related to the nucleus of the diagonal band of Broca, a nucleus with a strong projection to these two areas. As noted in the next paragraph, this nucleus shows prominent pathology in the autistic brain.

Another neuropathology noted in the brains of postnatal ASD individuals is abnormalities in neuronal size and evidence of neuronal loss. This has been found in the deep cerebellar nuclei, the inferior olive and nucleus of the diagonal band of Broca (NDB) in the septum **(**reviewed by Bauman and Kemper, 2005; Kemper and Bauman, 1998**)**. In all of the childhood ASD brains (ages 5-13 years), these neurons were consistently enlarged and appeared to be present in adequate numbers. In contrast, in the older brains, the cells of the fastigeal, globose and emboliform nuclei of the deep cerebellar nuclei and in the NDB were observed to be small and pale and reduced in number. In older individuals the neurons of the dentate and olivary nuclei, while small and pale, were not reduced in number. Neuronal swelling followed by atrophy and cell loss is an unusual neuropathology and is known to follow altered neuronal connectivity. For example, it has also been observed as a transneuronal event in the inferior olive following lesions of the central tegmental tract, a tract with a heavy projection to the inferior olive (Gautier and Blackwood, 1961). These abnormalities in cell size and number in the autistic brain are all intimately related to other areas of the brain with demonstrated early pathology and are presumed related to them **(**Kemper and Bauman, 1998, 2002**)**. In the case of the cerebellar nuclei and the inferior olive, these are intimately related to the Purkinje cell, a cell for which there is evidence of a prenatal

decrease in their number. The nucleus diagonal band of Broca is intimately related to the limbic system.

The density of neurons within multiple areas of the cerebral cortex in the ASD brain has been shown to be either unaffected (Coleman et al., 1985; Casanova et al., 2002) or slightly increased (Casanova et al., 2006).

In summary the majority of the neuropathological changes in the autistic that can be identified to specific periods of development, indicate a prenatal process. The exception to this are the changes that occur in cell size and number that occur at later stages of development. These can be understood in terms of earlier pathologies.

Abnormal postnatal brain growth

An unusually large head in individuals with autism, first noted by Kanner in 1943, has subsequently been repeatedly documented, with about 20% of the subjects with autism having head circumferences greater than the 97th percentile (Fombonne et al., 1999). Hobbs et al. (2007) in second trimester ultrasounds of 45 fetuses, later diagnosed as autistic, found that body size and head circumference were normal for gestational age. In a meta analysis of the literature on postnatal brain growth, Redcay and Courchesne (2005) found data on head circumference, autopsy brain weight, and brain volume determined by MRI for 531 autistic individuals. In these studies brain size was reliably estimated by measurements of head circumference for neonates, infants and young children and then by MRI and autopsy brain weights as head circumference becomes less reliable in older individuals. Fitted curves for head circumference and brain volume from 15 of these studies revealed a largely consistent pattern of age-related changes in brain size. Brain size was slightly reduced at birth, dramatically increased in size in the first postnatal year and then plateaued, with the majority of autistic individuals with a normal brain size by adulthood. There were thus two identified abnormalities in brain growth, an early abnormally rapid rate of brain growth followed by an abnormally slowed rate of brain growth.

Several studies have provided details on the timing of the abnormal postnatal brain growth during the first postnatal year. Hazlett (2007) obtained head circumferences at the time of their MRI studies and retrospectively from physician records for 113 autistic individuals and compared them to their own series of 189 typically developing (178) and developmentally disabled individuals (11). For the autistic individuals there was an average of four measurements per child. They reported the head circumference of the autistic individuals began to diverge at 12 months of age with the rate of head circumference growth then continuing to increase throughout the study period (up to 35 months). Dawson et al. (2006) obtained sequential physician recorded head circumferences (average 7 per subject) from 28 autistic individuals (17 with autism and 11 with PDD-NOS) and calculated the rate of increase from birth to 36 months. They concluded that the abnormal increased rate of head growth in head circumference was confined to the first 12 postnatal months. Further details of the timing have been documented in two studies. Courchesne et al. (2003) obtained physician-derived head circumferences from 48 children two to five years of age. Of these, 15 had data on head circumference at birth, at 1-2 months, at 3-5 months, and at 6-14 months. When

compared to published standards, they found a significant increase in head circumference at 6-14 months, with an increase in head circumference at 3-5 months that did not reach statistical significance. Dementieva et al. (2005) obtained physician recorded sequential head circumference measurements on 251 individual with well-documented autism. Fifteen of these had sufficient data to determine the rate of increase in head circumference growth from 0-1 month, from 2-6 months, and from 6-12 months. They found that the overgrowth was not present at birth, but that there was a "sudden and excessive" increase in head size between 1 and 2 months.

There is some data on the timing of the deceleration of brain growth and the time at which brain size becomes comparable to age-matched controls. In the study of Dawson et al. (2006), the rate of brain growth in ASD infants from birth to 36 months became comparable to controls from 12 to 36 months of age. According to Courchesne et al. (2003), maximum brain size occurs at 4-5 years and then becomes comparable to controls by adolescence and adulthood. Courchesne and Pierce (2005) found the maximum difference in brain size at 2-4 years, followed by a decline in difference in later childhood. Redcay and Courchesne (2005), in their meta analysis found an "abrupt cessation" in brain growth by 2-4 years followed by a plateau, with the age group 2-5 years with the greatest difference in brain size, Lainhart et al. (2006) suggested that the occurrence of macrocephaly reached its peak at 3-5 years of age and then remained stable. Aylward et al. (2002), in a MRI study of volume of 67 individuals ages 8-18, found an increased volume only in those less than 12 years of age.

Lainhart et al. (2006) pooled consistently recorded data on head circumferences from 338 well-documented individual with autism spectrum disorder, ages 2-49 years of age, from 10 centers in the NIH Collaborative Program of Excellence in Autism. In the entire group 17% were macrocephalic with 12-20% macrocephalic by 3-5 yrs, a rate that then remained stable. They found that head circumference of the autistic individuals showed a normally distributed curve, with a shift to the right, suggesting that the increase in head circumference affected the entire population. They noted that three other studies had not found a normally distributed head circumference (Lainhart et al., 1997; Fombonne et al., 1999; Miles et al., 2000), noting that these studies were all smaller, had more retarded individuals and included subjects that did not have idiopathic autism.

In summary, the available studies indicate that abnormal brain growth is a feature of the autistic brain. It begins shortly after birth with an accelerated rate of grain growth that begins as early as the first two postnatal months and, in some studies, continuing beyond the first postnatal year. There is then an abrupt, abnormal cessation of brain growth somewhere between 2-4 years of age with brain size then becoming comparable to controls in adolescence and adulthood.

Several studies that have examined the expected relationship between body length (height) and head size in autistic individuals and have failed to find evidence for this relationship (Lainhart et al., 1997, 2006; Miles et al., 2000; Courchesne et al., 2003; Hazlett et al., 2007; Dawson et al., 2006). It does appear to be related to parental head size with a striking incidence of macrocephaly in either parent (Stevenson et al. 1997; Miles et al., 2000; Lainhart et al., 2006). This occurs with both normocephalic and macrocephalic autistic individuals. In the study of Miles et al. (2000) the incidence of macrocephaly was a 45% in a parent of macrocephalic autistic individual and 37% with

normocephalic autistic individuals. This strikingly high incidence of increased head circumference in the first degree relatives suggests that hereditary factors may play a role.

No relationship of macrocephaly to intelligence has been found in several studies (Lainhart et al., 1997, 2006; Fombonne et al., 1999; Miles et al., 2000; Aylward et al., 2002: Sparks et al., 2002). However, Akshoomoff et al. (2004), in an analysis of 52 male ASD individuals and 15 controls noted that lower intellectual function in ASD was associated with an overall larger brain volume. In this study macrocephaly was singled out as a subgroup. Lainhart et al. (1997) found a weak correlation between a large head and the core features of autism as measured on the ADI, with the large head correlating with less severe features of autism. Courchesne et al. (2003) found that a larger number of individuals with autism had accelerated brain growth than those with PDD-NOS. Fombonne et al. (1999) and Miles et al. (2000) found no relationship with head size and the clinical features of autism.

Inflammatory changes in the ASD brain:

Vargas et al. (2005) studied the neuroinflammatory response in the cerebellum and cingulate and midfrontal cortices of 11 ASD brains, ages 5-44 years. They found evidence for a chronic, sustained innate immune response in all areas with the most marked response in the cerebellum and in the cerebrum in the subcortical white matter. This was associated with a microglial and astroglial response in all areas in association with cytokine response in both the brain and, in an independent study, in the cerebral spinal fluid. Astroglial cells were shown with double immunostaining to be a source of these cytokines. They noted that the microglial and astroglial response might be associated with neuronal and synaptic dysfunction and could provide a pathogenetic mechanism in the autistic brain. The etiology of this response was not identified, but had been previously noted in chronic degenerative diseases of the brain such as Alzheimer's disease, Parkinson's disease and HIV. They suggested that it might be a response to a neurotoxin, other environmental factors or to "…abnormal persistence of fetal patterns of development in response to genetic or environmental (eg, intrauterine, maternal) factors." These changes were not related to the age of the individual, history of epilepsy, developmental regression, or mental retardation. In contrast to the evidence for an innate immune response they found no evidence for an adaptive immune response, with a lack evidence for T and B cell activation, immunoglobulin deposition, or inflammatory infiltrates in the meninges or brain.

In a follow up paper, Pardo et al. (2005) discuss the role of immunity, neuroglia, and neuroinflammation in autism, mainly reviewing Vargas et al. (2005), They noted, "No clinical immune deficiency states have been reported in association with unusual infections or reactions to immunization, despite widespread interest in the possibility of such relationship," and that there is lack of proof that autism is an autoimmune disorder.

Two recent experimental studies suggest that innate immune response can occur at a timing that corresponds with that found during the second trimester in human (Rhodes et al., 2004; Zerrate et al., 2007). Both studies involved the injection of Terbutaline in rats on postnatal days 2, 5,11, and 14. The first two of these correspond in time to the second trimester of human pregnancy and the latter two to the third trimester. This drug, which readily crosses the placental barrier, has been extensively used to inhibit

preterm labor and has been associated with an increased incidence concordance of autism in dizygotic twins. Only injections on postnatal days 2 and 5 elicited a brisk astroglial (Rhodes et al., 2004) and microglial response (Zerrate et al., 2007), key changes in the innate immune response (Vargas et al., 2005).

Neurotoxicity of mercury:

The neurotoxicity of mercury has been extensively reviewed (i.e., Reuhl and Chang, 1979; Shiraki, 1979: Winship, 1986; Verity, 1997; Margos, 2001, 2003: Aschner and Walker, 2002; Clarkson and Magos, 2006; Nelson and Bauman, 2003). Most of what is known about the neurotoxicity of mercury in humans is from studies of methyl mercury (MeHg). Much less is known about ethyl mercury (EthylHg), the break down product of thimerosal (Clarkson and Magos, 2006; Nelson and Bauman, 2003; Burbacher et al., 2005).

The prominent clinical features of postnatal mercury toxicity include paresthesia, cerebellar ataxia, dysarthria, constriction of the visual fields and blindness (Clarkson and Magos, 2006; Winship, 1986; Shiraki, 1979), with paresthesia (involvement of peripheral nerves) the initial finding (Winship, 1986; Clarkson and Magos, 2006). Fetal exposure is associated with developmental abnormalities, cerebral palsy, blindness, deafness and mental retardation (Matsumoto et al., 1964; Choi et al., 1978; Winship, 1986). The corresponding neuropathological findings with postnatal mercury toxicity include involvement of peripheral sensory nerves (Eto et al., 1978, 2002; Verity, 1997; Shiraki 1979), the cerebellar cortex with marked loss of granule cells and relatively preserved Purkinje cells (Clarkson and Magos, 2006; Verity, 1997; Shiraki, 1979), and the cerebral cortex with a loss of neurons and myelinated fibers associated with glial proliferation (Shiraki, 1979; Eto et al., 1978, 2002). The pattern of neuropathology in infants exposed to mercury is similar to that of the adult with, however, less involvement of the cerebellum and more involvement of the cerebral cortex (Reuhl and Chang, 1979; Shiraki, 1979). As an example of this Takeuchi et al. (1979) reported five childhood cases with Minamata disease with severe involvement of the cerebral cortex and the clinical picture of a decerebrate syndrome, findings that have not been noted in adult cases. With prenatal exposure there is even more widespread involvement of the cerebral cortex, relative sparing of the cerebellum, and disturbances in neuronal migration and malformations (Matsumoto et al., 1964; Choi et al., 1978; Reuhl and Chang, 1979).

A striking feature of neuropathology of mercury toxicity is the predilection for specific loci and specific cell types within its areas of vulnerability. The pathology in the cerebral cortex is most marked in the visual cortex with some involvement of the superior temporal cortex and other cortical areas (Nierenberg et al., 1998; Verity, 1997; Shiraki, 1979; Takeuchi et al., 1979). Shiraki (1979) noted that the visual cortex was involved in all 17 cases that he examined. An example of a relatively preserved area is the hippocampus. Both Matsumoto et al. (1964) and Chio et al. (1978) have reported a lack of involvement the hippocampus and Takeuchi et al. (1979) involvement in only one of five brains. Within the visual cortex, it characteristically involves the depth of the calcarine fissure, with resultant tunnel vision, and the neuronal loss shows a predilection for layer II and the upper part of layer III (Shiraki, 1979; Takeuchi et al., 1979). In the cerebellum the area of predilection is for the depths of the sulci in the midline (nodulus,

uvula, lingual, and medial parts of the semilunar nodule), and within the involved areas, a marked loss of granule cells with relative preservation of Purkinje cells (Matsumoto et al., 1964; Verity, 1997; Eto et al., 1978; Shiraki, 1979; Reuhl and Chang, 1979; Takeuchi et al., 1979; Clarkson and Magos, 2006). Shiraki (1979) noted that the cerebellum was involved in almost all of the 17 cases that he examined. The deep cerebellar nuclei and the inferior olive, which are synaptically related to the cerebellar cortex, were reported to be unremarkable by Chio et al. (1978) and Eto et al. (1978). These four brains were from infants with fetal exposure to mercury. Peripheral nerve involvement is focused on the sensory, rather than the motor nerves, with involvement of the dorsal spinal roots, relative sparing of the dorsal root ganglia, and peripheral nerves showing loss of myelinated fibers, Schwann cell proliferation and increased connective tissue (Reuhl and Chang, 1979; Shiraki, 1979; Takeuchi et al., 1979; Eto et al., 1978, 2002; Verity, 1997). In a study of 83 autopsied cases of Minamata disease, Eto and Takeuchi (1978) found peripheral nerve lesions in all cases. Shiraki (1979) noted that in these cases the anterior horn cells are preserve and there was little involvement of the anterior (motor) roots.

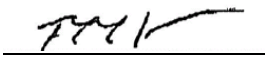
Amin-Zaki et al. (1981), in a five year follow up of 28 Iraqi children exposed to mercury from mother's milk, noted a normal head circumference without evidence of microcephaly. These mothers had consumed tainted bread for a 1-3 month period. Many of these children showed delayed motor and speech development. In more severely involved individuals, Shiraki (1979) reported that the brains were unusually small. There is no mention in this literature of increased brain weight or abnormally enlarged neurons.

It can be seen from this review of the literature on postnatal mercury toxicity that it is associated with loss of specific types of neurons in specific locations in the brain. The areas of predilection in the cerebral cortex is the visual cortex where it primarily affects this cortical area in the depth of the calcarine sulcus with the most severe neuronal loss in layer II and upper part of layer III. In the cerebellum the area of predilection is the midline (vermal) part with the neuronal loss mainly in the depths of the sulci and primarily affects the granule cells with relative preservation of the Purkinje cell. In both the cerebral cortex and the cerebellum, the pathology is associated with a glial response. In the peripheral nervous system the predilection is for the sensory nerves, with little evidence of involvement of the motor nerves. As can be seen on the section on the neuropathology, these pathologies are not a feature of the autistic brain. In the autistic brain there is no evidence for a postnatal destructive lesion in the cerebral cortex and studies of neuronal density show no evidence of a decrease in density of neurons. Instead, in the cerebral cortex of autistic individuals, there is abundant evidence for developmental disturbances that can be dated to the prenatal period. These malformations resemble the lesions seen in prenatal mercury toxicity. Further, the characteristic tunnel vision noted in mercury toxicity has not been noted in autistic individuals (reviewed by Nelson and Bauman, 2003).

Both autism and mercury toxicity share an involvement of the cerebellum. However, the area of predilection is different. In the autistic brain it is the posterior aspect of the lateral lobes and in mercury toxicity the midline structures. With mercury toxicity the depths of the sulci area preferentially involved, a feature not found in the autistic brains. Further, with mercury toxicity the most marked involvement is loss of granule cells with relative preservation of Purkinje cells. In the autistic brain the most marked involvement in the cerebellar cortex is a decrease number of Purkinje cell with

granule cells lost only in those brains with marked Purkinje cell loss. The relationship between the number of granule cells and the number of Purkinje cells noted in the autistic brain has been elucidated in rat studies. With early loss of Purkinje cells the number of granule cells is adjusted such that the ratio of Purkinje cells to the number of granule cells is maintained (Chen and Hilman, 1989; Fonnum and Lock, 2000). In these experimental studies a loss of granule cells is not associated with a concomitant loss of Purkinje cells, the situation noted above in mercury toxicity. Involvement of the peripheral sensory nerves and the classical clinical manifestations of cerebellar lesions, a prominent feature of mercury toxicity, have not been observed in autistic individuals (Nelson and Bauman (2003).

There is also lack of support for an effect of mercury on neuropsychological functioning. Thompson et al. (2007), in a study the possible effect of thimerosal exposure on neuropsychological outcomes in 1047 children between 7 and 10 years of age, concluded the was no support for a causal association between early exposure to thimerosal and defects in neuropsychological functioning. Earlier, similar studies by Heron and Golding (2004) and Andrews et al. (2004), with respectively 12,956 and of 103,043 thimerosal-exposed children came to a similar conclusion.



Thomas L. Kemper

Date 2/21/08

References:

Akbarian S, Kim JJ, Potkin SO, Hetrick WP, Bunney WE Jr, Jones EG. (1996) Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. Arch Gen Psychiatry 53:425-436

Amin-Zaki L, Majeed MA, Greenwood MR, Elhassani SB, Clarkson TW, Doherty RA (1981) Methylmercury poisoning in the Iraqi suckling infant: longitudinal study over five years. J Appl Toxic 1:210-214.

Andrews N, Miller E, Grant A, Stowe J, Osborne V, Taylor B. (2004) Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a causal association. Pediatrics 114:584-591.

Aschner M, Walker SJ. (2002) The neuropathogenesis of mercury toxicity. Mol Psychiatr 7:S40-41.

Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N (2002) Effects of age on brain volume and head circumference in autism. Neurology 59:175-183.

Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P. (1998) A clinicopathological study of autism. Brain 121:889-905.

Bauman ML, Kemper TL (1994) Neuroanatomical observations of the brain in autism. In: Bauman ML, Kemper TL (eds) The Neurobiology of Autism . The Johns Hopkins University Press, Baltimore pp 119-145.

Bauman ML, Kemper TL (2005) Structural brain anatomy in autism: What is the evidence? In: Bauman ML, Kemper TL (eds) The Neurobiology of Autism. The Johns Hopkins University Press, Baltimore pp121-135.

Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, Clarkson T (2005) Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing Thimerosal. Eviron Health Perspectives 113:1015-1021.

Casanova MF (2007) The neuropathology of autism. Brain Pathol 17:422-433.

Casanova MF, van Kooten IAJ, Switala AE, van Engeland H, Heinsen H, Steinbusch HWM, Hof PR, Trippe J, Stone J, Schmitz, C (2006) Minicolumnar abnormalities in autism. Acta Nuropathol 112:2287-303.

Casanova MF, Buxhoeveden D, Switala A, Roy E (2002) Minicolumnar pathology in autism. Neurology 58:428-432.

Centers for Disease Control and Prevention (1998) Measles, mumps, and rubella – Vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR 47:1-57.

Clarkson TW, Magos L (2006) The toxicology of mercury and its chemical compounds. Critical Reviews in Toxicology 36:609-662.

Chen S, Hillman DE (1989) Regulation of granule cell number by a predetermined number of Purkinje cells in development. Dev Brain Res Dev Brain Res 45:137-147.

Choi BH, Lapham L, Amin-Zaki L, Saleem T (1978) Abnormal neuronal migration, deranged cerebral cortical organization, and diffuse white matter astrocytosis of human fetal brain: a major effect of methylmercury poisoning in utero. J Neuropath Exp Neurol 37:719-733.

Coleman PD, Romano J, Lapham L, Simon W (1985) Cell counts in cerebral cortex in an autistic patient. J Autism Dev Disord 15:245-255.

Courchesne E, Carper R, Askhoomoff N (2003) Evidence of brain overgrowth in the first year of life in autism. JAMA 290:337-344.

Dawson G, Munson J, Webb SJ, Nalty T, Abbott R Toth K. (2006) Rate of head growth decelerates and symptoms worsen in the second year of life in autism. Biol Psychiatry 61:458-464.

Dementieva YA, Vance DD, Donnelly SL, Elston LA, Wolpert CM, Rvan SA, DeLong R, Abramson RK, Wright HH, Cuccaro ML (2005) Accelerated head growth in early development with autism. Pediatric Neurology 32:102-108.

Dvorak K, Feit J (1977) Migration of neuroblasts through partial necrosis of the cerebral cortex in newborn rats – contribution to the problem of morphological development and developmental period of cerebral microgyria. Acta Neuropathol 38:203-212.

Dvorak K, Feit J, Jurankova Z (1978) Experimentally induced focal microgyria and status verucosus deformis in rats – pathogenesis and interaction. Histological and autoradiographic study. Acta Neuropathol 44:121-129.

Eastwood SL, Harrison PJ (2003) Interstitial white matter neurons express less reelin and are abnormally distributed in schizophrenia: towards an integration of molecular and morphologic aspects of the neurodevelopmental hypothesis. Mol Psychiatry 821-31.

Eastwood SL, Harrison PJ (2005) Interstitial white matter neuron density in the dorsolateral prefrontal cortex and parahippocampal gyrus in schizophrenia. Schizophr Res 79:181-188.

Eto K, Takeuchi T (1978) A pathological study of prolonged cases of Minamata disease. Acta Path Jap 28:565-584.

Eto K, Tokunaga H, Nagashima K, Takeuchi T (2002) An autopsy case of minamata disease (methylmercury poisoning)--pathological viewpoints of peripheral nerves. Toxicol Pathol 30:714-22.

Fombonne E, Roge B, Claverie J, Courty S (1999) Microcephaly and macrocephaly in autism. J Autism Dev Dis 29:113-119.

Gautier JC, Blackwood W. Enlargement of the inferior olivary nucleus in association with lesions of the central tegmental tract or dentate nucleus. Brain 1961;84:341-364.

Fonnum F, Lock EA (2000) Cerebellum as a target for toxic substances. Toxicol Lett 112-113:9-16.

Harding B, Copp AJ (1997) Malformations In: Graham DI, Lantos P (eds) Greenfield's Neuropathology, 6th edition. Arnold, London. Pp397-536.

Hazlett HC, Poe M, Gerig G, Smith RG, Provensale J, Ross A, Gilmore J, Piven J. (2007) Magnetic resonance Imaging and head circumference study of brain size in autism. Birth through age 2 years. Arch Gen Psychiatry 62:1366-1376.

Heron J, Golding J. (2004) Thimerosal exposure in infants and developmental disorders: a prospective cohort study in the United Kingdom does not support a causal association. Pediatrics 114:577-583.

Hobbs K, Kennedy A, DuBray M, Bigler ED, Peterson PB, McMahon W (2007) A retrospective fetal ultrasound study of brain size in autism. Biol Psychiatry 62:1048-1055.

Holmes G, Stewart TG. On the connection of the inferior olives with the cerebellum in man. Brain l908;31:125-37.

Hutsler JJ, Love T, Xhang H (2006) Histological and magnetic resonance imaging assessment of cortical layering and thickness in autism spectrum disorders. Biol Psychiatry 61:449-457.

Kanner L (1943) Autistic disturbances of affective contact. Nervous Child 2:217-250. (not at Countway – volume 2 missing)

Kemper, T.L. and Bauman, M.L. (1998) Neuropathology of infantile autism. J. Neuropathol. Exp. Neurol. 57:645-652.

Kemper, T.L, and Bauman, M.J. (2002) Neuropathology of Infantile Autism. Molecular Psychiatry. 7:S12-S13.

Kostovic I, Rakic P. (1990) Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. J Comp Neurol 297:441-70.

Lainhart JE, Bigler ED, Bocian M, et al. (2006) Head circumference and height in autism: a study by the Collaborative Program of Excellence in Autism. Am J Med Genet Part A 140A:2257-2274.

Lainhart JE, Piven J, Wzorek M, Landa R, Santangelo SL, Coon H, Folstein SE. (1997) Macrocephaly in children and adults with autism. J Am Acad Child Adolesc Psychiatry36:282-290.

Marin-Padilla M (1988) Early ontogenesis of the human cerebral cortex, IN: Peters A, Jones EG (eds) Cerebral Cortex Vol 7 pp1-34.

Matsumoto H, Koya G, Takeeuchi T (1964) Fetal minamata disease J Neuropath Exp Neurol 24:563-574.

Miles JH, Hadden LL, Takahashi TN, Hillman RE (2000) Head circumference is an independent clinical finding associated with autism. Amer J Med Genetics 95:339-350.

(PDF in HC folder) Miller MT, Strömland K, Ventura L, Johansson M, Bandim JM, Gillberg C (2005) Autism associated with conditions characterized by developmental errors in early embryogenesis: a mini review. Int J Dev Neurosci 23:201-219.

Matsumoto H, Koya G, Takeeuchi T (1964) Fetal minamata disease J Neuropath Exp Neurol 24:563-574.

Nelson KB, Bauman ML (2003) Thimerosal and autism? Pediatrics 111:674-679.

Nierenberg DW, Nordgren RE, Chang MB, Siegler RW, Blayney MB, Hochberg F, Toribara TY, Cernichiari E, Clarkson T. (1998) Delayed cerebellar disease and death after accidental exposure to dimethylmercury. NEJM 338:1672-1676.

Norman RM. Cerebellar atrophy associated with etat marbre of the basal ganglia. J Neurol Psychiatry l940;3:311-318.

Okhotin VE Kalinichenko SG (2003) Subcortical white matter interstitial cells: their connections, neurochemical specialization, and role in the histogenesis of the cortex. Neurosci Behav Physiol 33:177-193.

Palmen SJMC, van Engeland H, Hof PR, Schmitz C (2004) Neuropathological findings in autism, Brain 127:1-12.

Pardo CA, Vargas DL, Zimmerman AW (2005) Immunity, neuroglia and neuroinflammation in autism. Int Rev Psychiatry. 17:485-495.

Rakic P (1988) Defects of neuronal migration and the pathogenesis of cortical malformations. Prog Brain Res 73:15-37.

Rakic P (1995) A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during gestation. TNS 18:383-388.

Rakic P, Sidman RL. (1970) Histogenesis of cortical layers in human cerebellum particularly the lamina dissecans. J Comp Neurol139:473-500.

Raymond J, Bauman ML, Kemper T L (1996) The hippocampus in autism: Golgi analysis. Ann Neurol 26:483-484.

Redcay E, Courchesne E (2005) When is the brain enlarged in autism? A meta-analysis of all brain size reports. Biol Psychiatry 58:1-9.

Reuhl KR, Chang LW (1979) Effects of methylmercury on the development of the nervous system: a review. Neurotoxicology 1:21-55.

Rhodes MC, Seidler FJ, Abdel-Rahman A, Tate CA, Nyska A, Rincavage HL, Slotkin TA (2004) Terbutaline is a developmental neurotoxicant: effect on neuroproteins and morphology in cerebellum, hippocampus, and somatosensory cortex. J Pharm and Exp Therapeutics 308:529-537.

Rodier PM, Ingram JL, Tisdale B, Nelson S, Roman J. (1996) Embryological origins for autism: developmental anomalies of the cranial nerve nuclei. J Comp Neurol 370:247-61.

Rodier PM, Hyman SL (1998) Early environmental factors in autism. Ment Retard Dev Dis Res Reviews 4:121-128.

Shiraki H (1979) Neuropathological aspects of organic mercury intoxication, including Minamata disease. In; Handbook of Clinical Neurology, Vinken PJ, Bruyn, GW, eds. Vol 36, Amsterdam: North-Holland Publishing Co. pp 83-145.

Sidman RL, Rakic, P (1982) Development of the human central nervous system. In: Histology and Histopathology of the Nervous System. Haymaker W, Adams RD (eds.) Charles C Thomas, Springfield, Illinois. Pp 3-145.

Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA, Maravilla KR, Giedd JN, Munson J, Dawson G, Dager SR (2002) Brain structural abnormalities in young children with autism spectrum disorder. Neurology 59:184-192.

Stevenson RE, Schroer RJ, Skinner C, Fender D, Simensen RJ (1997) Autism and macrocephaly. Lancet 349:1744-1745.

Takeuchi T, Eto N, Eto K (1979) Neuropathology of childhood cases of mercury poisoning (Minamata disease) with prolonged symptoms, with particular reference to the decortication syndrome. Neurotoxicology 1:1-20.

Thompson WW, Price C, Goodson B, et al. (2007) Early thimerosal exposure and neuropsychological outcomes at 7 and 10 years. NEJM 357:1281-1292.

Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo C (2005) Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 57:67-81.

Verity MA (1997) Toxic Disorders. In; Greenfield's Neuropathology, 6th edition, Graham DI, Lantos PL (Eds.) Arnold, London, Sydney, Auckland, pp 755-810.

Zerrate MC, Pletnikov M, Connors SL, Vargus DL, Seidler FJ, Zimmerman AW, Slotkin TA, Pardo CA (2007) Neuroinflammation and behavior abnormalities after neonatal Terbutaline treatment in rats: implication for autism. J Pharm and Exp Therapeutics 322:16-22.